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Cost-effectiveness of eplerenone in patients with left ventricular dysfunction after myocardial infarction - an analysis of the EPHEsus study from a Swiss perspective

Szucs, T D ; Holm, M V ; Schwenkglenks, M ; Zhang, Z ; Weintraub, W S ; Burnier, M ; Erne, P

Abstract: **OBJECTIVE:** The EPHEsus study demonstrated that aldosterone blockade with eplerenone decreased mortality in patients with left ventricular systolic dysfunction (LVSD) and heart failure after acute myocardial infarction (AMI). The EPHEsus pharmacoeconomic analysis was performed to evaluate the cost-effectiveness of eplerenone in the Swiss setting. **MATERIALS AND METHODS:** A total of 6,632 patients with LVSD and heart failure after AMI were randomized to eplerenone or placebo and followed for a mean of 16 months. The co-primary endpoints were all-cause death and the composite of cardiovascular death/cardiovascular hospitalization. The evaluation of resource use included hospitalizations, outpatient services, and medications. Survival beyond the trial period was estimated using data from the Framingham Heart Study, the Saskatchewan Health database, and the Worcester Heart Attack Registry. The incremental cost-effectiveness of eplerenone in cost per life-year and quality-adjusted life-year gained was estimated. The perspective of the Swiss third party payers was used. Daily treatment costs of eplerenone were set at CHF 3.88. All other resources were valued on the basis of official tariffs. Discounting of the results was performed at a rate of 3%. **RESULTS:** The number of life-years gained with eplerenone was 0.1083 based on Framingham, 0.0661 with Saskatchewan and 0.1518 with Worcester survival estimates. Total costs were CHF 1,028 higher over the trial period in the eplerenone arm, due to drug cost. The incremental cost-effectiveness ratio was CHF 10,145 per life-year gained with Framingham, CHF 16,178 with Saskatchewan, and CHF 7,693 with Worcester survival estimates. The corresponding costs per QALY were CHF 15,219, CHF 23,965 and CHF 11,337, respectively. **CONCLUSION:** Eplerenone is effective in reducing mortality and, in Switzerland, is also cost-effective in increasing years of life for patients with LVSD after AMI.

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Cost-Effectiveness of Eplerenone in Patients with Left Ventricular Dysfunction after Myocardial Infarction—An Analysis of the EPHEsus Study from a Swiss Perspective

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Abstract

Objective The EPHEsus study demonstrated that aldosterone blockade with eplerenone decreased mortality in patients with left ventricular systolic dysfunction (LVSD) and heart failure after acute myocardial infarction (AMI). The EPHEsus pharmacoeconomic analysis was performed to evaluate the cost-effectiveness of eplerenone in the Swiss setting.

Materials and methods A total of 6,632 patients with LVSD and heart failure after AMI were randomized to eplerenone or placebo and followed for a mean of

16 months. The co-primary endpoints were all-cause death and the composite of cardiovascular death/cardiocirculatory hospitalization. The evaluation of resource use included hospitalizations, outpatient services, and medications. Survival beyond the trial period was estimated using data from the Framingham Heart Study, the Saskatchewan Health database, and the Worcester Heart Attack Registry. The incremental cost-effectiveness of eplerenone in cost per life-year and quality-adjusted life-year gained was estimated. The perspective of the Swiss third party payers was used. Daily treatment costs of eplerenone were set at CHF 3.88. All other resources were valued on the basis of official tariffs. Discounting of the results was performed at a rate of 3%.

Results The number of life-years gained with eplerenone was 0.1083 based on Framingham, 0.0661 with Saskatchewan and 0.1518 with Worcester survival estimates. Total costs were CHF 1,028 higher over the trial period in the eplerenone arm, due to drug cost. The incremental cost-effectiveness ratio was CHF 10,145 per life-year gained with Framingham, CHF 16,178 with Saskatchewan, and CHF 7,693 with Worcester survival estimates. The corresponding costs per QALY were CHF 15,219, CHF 23,965 and CHF 11,337, respectively.

Conclusion Eplerenone is effective in reducing mortality and, in Switzerland, is also cost-effective in increasing years of life for patients with LVSD after AMI.

Key words cost-effectiveness · medical economics · heart failure · eplerenone · ephesus

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Introduction

Population studies, together with data derived from medical records, reveal a range of estimated heart failure (HF) prevalence of 1–10% [1]. In the general European population, the prevalence of symptomatic heart failure ranges from 0.4 to 2% [2]. The European Society of Cardiology estimates that approximately 10 million patients suffer from heart failure in Europe [3]. Estimated incidence rates vary from approximately 0–1% per annum. Reasons for variation include age, sex and, possibly, methodology. In community studies, the 5-year mortality is between 50–60% while, in patients requiring hospital admission, the annual mortality is 10–20% in those with mild–moderate symptoms, and as high as 40–60% in severe HF. While angiotensin-converting enzyme (ACE) inhibitor treatment does significantly reduce mortality in all grades of symptomatic HF, the annual mortality in severe patients (i.e., New York Heart Association [NYHA] Class IV) remains above 50% [4].

Evidence from studies based in the general population, general practice and hospital strongly suggests an emerging epidemic of HF in Europe [5]. Notably, a further increase in the prevalence of the syndrome in the elderly is expected in the next decades. The majority of men and women with left ventricular systolic dysfunction is asymptomatic. In people diagnosed with HF, sudden cardiac death occurs 6–9 times the rate of the general population.

Several cost of illness and cost of care analyses suggest that HF poses a great economic burden to health care providers and society as a whole [8]. HF is the single most frequent cause of hospitalization for people aged 65 and older. In Switzerland the burden of heart failure has been determined by Szucs et al [6]. Using patient chart reviews, the annual costs was CHF 10,637 across all patients, CHF 3,951 in NYHA class I and II patients, CHF 8,727 in class III patients and CHF 13,162 in class IV patients. These figures yielded a total expenditure of at least CHF 649 million annually. This corresponds to 1.6% of total Swiss health spending [6, 7].

The US Food and Drug Administration (FDA) has approved the aldosterone receptor blocker eplerenone for improving the survival of stable patients with left ventricular systolic dysfunction (LVSD, i.e., ejection fraction <40%) and clinical evidence of HF after acute myocardial infarction (MI). More than one-third of MI survivors develop HF, and when they do, their 5-year mortality rate is 50%. FDA approval of the drug was based on results of the EPHEsus (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study) trial. Compared with post-MI HF patients on placebo and

standard therapy (ACE inhibitors and beta-blockers), eplerenone on top of standard therapy, reduced mortality significantly by 15%.

To use the existing resources optimally, the cost-effectiveness of the different treatments must be taken into consideration. If the same cost-effectiveness endpoints are used (e.g., costs per life-year saved), it is possible to compare treatments across various indications. Although a US economic evaluation of the EPHEsus trial has become available recently [8], it is still required by national Swiss policy makers to obtain cost-effectiveness estimates adapted to the particular situation in Switzerland.

Study objective

The purpose of this study is to assess the cost-effectiveness of eplerenone in patients with LVSD after MI from the perspective of the Swiss healthcare system.

Materials and methods

Study design

A cost-effectiveness analysis was chosen for this study, i.e., the numerator is expressed as incremental costs and the denominator as incremental life-years. In summary, we planned to calculate incremental costs per life-year gained and incremental costs per quality-adjusted life-year (QUALY) gained through treatment with eplerenone in Switzerland. All costs are expressed in Swiss francs (CHF).

The present analysis is retrospective and is based on the results of the double-blind, randomised, controlled clinical trial EPHEsus (Table 1) which was conducted in Europe, Latin America, USA and Canada [9]. It was assumed that the clinical findings of EPHEsus can be transferred to Switzerland.

EPHEsus was designed to assess whether eplerenone has a beneficial effect on morbidity and mortality in patients with MI complicated by HF. A total of 6,642 patients with MI, left ventricular ejection fraction (LVEF) \leq 40%, and symptoms of HF, who were already on standard therapy, were randomly assigned to 25 or 50 mg of eplerenone, or placebo, once daily [2]. For standard therapy, 87% of patients were receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), 75% were taking beta-blockers, 88% were taking aspirin, and 60% were taking diuretics. Patient characteristics at baseline were similar between the eplerenone and placebo groups.

Table 1 Design of the EPHESUS study [20]

Objectives	To establish whether the treatment with eplerenone, an aldosterone blocker that selectively blocks the mineralocorticoid receptor reduces overall mortality or hospitalization for cardiovascular events among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure who are receiving optimal medical therapy.
Study design	Multicentre, double blind, randomised, placebo-controlled study in 674 centers and 37 countries in Europe, Latin America, the United States and Canada.
Inclusion criteria	Acute myocardial infarction Left ventricular dysfunction with LVEF <40% Heart failure Diabetics with LVEF <40% without symptoms of heart failure
Exclusion criteria	Use of potassium sparing diuretics Serum creatinine >2.5 mg/dl Serum potassium >5 mmol/l
Intervention	Treatment initiation 3–14 days after a myocardial infarction Eplerenone 25 mg/d, titrated to 50 mg/d or placebo
Endpoints	<i>Primary:</i> time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including heart failure, recurrent AMI, stroke, or ventricular arrhythmia. <i>Secondary:</i> cardiovascular death or cardiovascular hospitalisation
Period of observation	Until 1,012 deaths occurred

During follow-up there were statistically significant reductions in both primary endpoints, with 478 deaths in the eplerenone group and 554 deaths in the placebo group, a 15% reduction in total all-cause mortality (RR 0.85, $P = 0.008$) and 13% fewer cardiovascular-related deaths and cardiovascular hospitalizations (RR 0.87, $P = 0.002$) compared with the placebo group. Resource information over the course of follow-up was recorded prospectively on standardized form and entered into a computerized database.

A brief comparison of the effects on clinical outcomes of the EPHESUS study for the eplerenone and placebo groups with respect to some particularly cost-relevant clinical events is shown in Table 2. A detailed description of study design and results has been published previously [10].

Calculation of costs and effectiveness

General considerations

Treatment costs for patients in the eplerenone and placebo arms of EPHESUS were calculated by multiplying study-wide resource utilization measures collected in the trial by their corresponding local unit costs, which were collected outside the trial. For this study we universally apply Swiss unit costs to calculate the incremental costs of eplerenone usage.

In EPHESUS resource utilization information was collected on the following services: hospitalizations (for any cause); emergency room (ER) visits; major outpatient diagnostic procedures and tests; concomitant medications; and eplerenone.

Table 2 Comparison of treatment effects in the EPHESUS study [9]

	Eplerenone ($n = 3,319$)	Placebo ($n = 3,313$)	P value
Baseline characteristics			
Age (mean years)	64.2 ± 11.3	64.7 ± 11.7	0.14
Women (%)	28.3	29.6	0.26
Prior myocardial infarction (%)	27.4	26.8	0.52
Diabetes (%)	32.3	32.3	0.95
Hypertension (%)	59.7	61.2	0.22
History of heart failure (%)	14.2	15.2	0.24
Ejection fraction (mean percent)	33.1 ± 6.0	33.0 ± 6.1	0.55
Primary endpoints			
Death (any cause) (%)	14.4	16.7	0.008
Death or hospitalization for cardiovascular events (%)	26.7	30.3	0.002
Secondary endpoints			
Death from any cause or any hospitalization (%)	52.1	55.2	0.02
Death from cardiovascular causes (%)	12.3	14.6	0.005

Resource utilization data were collected from all patients enrolled in the trial from randomization the end of the trial or death, whichever occurred first. Mean resource utilization by service category and treatment arm was calculated in the first, second and third years following randomization on an intent-to-treat basis.

Hospitalizations

Two independent physicians who were blinded with respect to therapy assigned one or more applicable Diagnosis Related Group (DRG) codes to each hospitalization based on the reasons for admission. In cases where multiple DRGs were recorded for a particular hospitalization the DRG with the highest unit cost was assigned to that hospitalization [11]. Imputation procedures were applied in order to address differences between US and non-US countries of the clinical trial. Trial-wide utilization rates are presented in Table 3.

Emergency room visits, diagnostic procedures and tests

Each recorded emergency room visit and outpatient diagnostic procedure/test in EPHESUS was assigned to a unique code by the two blinded physicians. On this basis, a similar procedure as for the hospitalizations was used to assign costs. Trial-wide utilization rates are presented in the Table 4.

Eplerenone and concomitant medication

Concomitant medications used in the cost-effectiveness analysis were limited to the 42 most commonly observed in EPHESUS. There were 1,434 concomitant medications recorded by the EPHESUS investigators. Of these,

Table 3 Utilization rates for hospitalisation

DRG	Trial-wide mean utilization
Specific cerebrovascular disorders except TIA	0.0243
Coronary bypass with PTCA	0.0025
Coronary bypass with cardiac catheterization	0.0841
Percutaneous cardiovascular procedures	0.0418
Other permanent cardiac pacemaker implant or PTCA coronary stenting	0.0137
Circulatory disorders with AMI without major complications, alive	0.0703
Heart failure and shock	0.2260
Cardiac arrhythmias & conduction disorders without complications	0.0397
Angina pectoris	0.1428

Table 4 Utilization rates for emergency room visits, procedures and tests

Resource	Trial-wide mean utilization
Pacemaker, insertion or replacement of pacemaker pulse generator only; single chamber, atrial or ventricular	0.0068
Insertion or repositioning of electrode lead(s) for single or dual chamber pacing cardioverter-defibrillator and insertion of pulse generator	0.0035
Myocardial perfusion imaging; (planar) single study, at rest or stress (exercise or pharmacologic), with or without quantification	0.0882
Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel	0.0063
Percutaneous transluminal coronary balloon angioplasty; single vessel	0.0069
Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; tracing only without interpretation and report	0.1599
Electrocardiographic monitoring for 24 h by continuous original ECG waveform recording and storage, and visual superimposition scanning, recording.	0.0706
Right heart catheterization	0.0045
Left heart catheterization	0.1484
Electrophysiologic follow-up study with pacing and recording to test effectiveness of therapy, including induction or attempted induction of arrhythmia	0.0097

42 had at least 100,000 days of use or were the most common representative of their class of cardiac-related medications (e.g., clonidine among alpha-blockers). These 42 medications represented approximately three-fourths of the total concomitant medication days in the trial.

For eplerenone and each of these concomitant medications, trial-wide mean utilization (days) in the first, second and third years following randomization was multiplied by its corresponding, country-specific cost per day to arrive at total costs in each period. The discounted present value of these over the three time periods was then used in the ICER calculation.

Swiss unit costs

Swiss unit cost data for hospitalizations were derived by utilizing the All Patient Diagnostic Related Groups

(AP-DRGs) [12], which are currently being implemented throughout Switzerland. Costs for outpatient procedures and tests were derived from the national tariff code TARMED [13]. The resource use compositions of the TARMED codes did not exactly correspond to those of the codes assigned by the blinded physician reviewers, that were reported in EPHESUS. Using the available TARMED codes, approximations were therefore used in many cases approximated to match the identified codes. Current concomitant medications prices were calculated on the basis of the Swiss Pharmaceutical Compendium and of average daily recommended dosages [14]. Pharmaceutical consumption in hospitals is included in the AP-DRG costs for the corresponding procedure. Prices are 2005 prices. All unit costs are displayed in Tables A1–A3 in the [Appendix](#).

Eplerenone unit cost

As the final prescription price of eplerenone was not yet available at the time of this study, a most likely estimate of CHF 3.88 per day (public price) was used in the base case. A patient co-payment of 10% was deducted from the pharmacy price, as this is mandatory for all outpatient medication prescriptions in Switzerland. These total medication costs were projected assuming a patient compliance rate of 100% throughout the treatment period.

Total costs

The resource utilization and unit cost information described above was used to calculate the discounted present value of treatment costs for all patients in the eplerenone treatment arm and placebo arm of EPHESUS as follows: total costs by type of service for each of the 3 years following randomization were calculated by multiplying unit costs for each hospitalization, ER visit, diagnostic procedures/test, concomitant medication and eplerenone by their corresponding mean utilization values for the first, second and third year following randomization. (By definition, eplerenone utilization is zero for patients in the placebo arm of the trial.) These costs were discounted by 3%. Discounted costs were then summed over type of service (e.g., hospitalizations, ER visits, diagnostic procedures/tests, concomitant medications and eplerenone), by treatment arm (eplerenone or placebo).

Cost for HF hospitalizations, CV hospitalizations (primary endpoint based) and all CV hospitalizations were calculated from *all* hospitalizations where these

conditions were recorded as a DRG, whether or not they were the most expensive DRG for that hospitalization. This method for computing costs is identical to the method used to measure condition-specific utilization in the published results of EPHESUS.

Effectiveness

Effectiveness was measured using two metrics: life years gained; and QALYs. Life years gained was defined as the expected number of years before death at randomization (life expectancy) minus the observed number of years before death following randomization. Patients who did not die during the trial were assumed to reach their life expectancy and, therefore, had no life years lost. All life years lost estimates were discounted using rates from 0–6%.

Life expectancy estimates were obtained from epidemiology studies conducted in different databases and adjusted to specific Swiss life-expectancies. The ideal data source from which to estimate lost life expectancy would include longitudinal data, a large cohort of patients, patients with similar characteristics to those in EPHESUS, and would be widely known and acknowledged as credible. Because no single data source perfectly met all these criteria, the following three data sources were used to estimate survival:

Framingham heart study

The estimated age and gender-specific life expectancy for patients with congestive heart failure was published from the Framingham Heart Study database [15, 16, 17]. The patient population for these estimates was drawn from patients randomly enrolled in the original study cohort between 1948 and 1951 with no cardiovascular disease upon enrollment.

It should be pointed out that the population used to derive these life expectancy estimates differs from the population in EPHESUS in two ways. First, life expectancy is based on conditions in the 40 year follow-up period after enrollment, which are unlikely to be similar to conditions patients face currently. Second, the Framingham analysis is based on patients who have heart failure, whereas EPHESUS patients had heart failure following MI.

Saskatchewan health

The Saskatchewan Health dataset contains administrative health care claims for residents of the province

of Saskatchewan, Canada [18]. These data were used to estimate a statistical model of life expectancy as a function of the patient's age, gender and history of diabetes, MI, ischemic stroke, hypertension and HF.

Worcester heart attack study

The Worcester Heart Attack Study is an ongoing, population-based study of myocardial infarction (MI) [19, 20]. Patients are enrolled biannually from medical centers in the Worcester, MA metropolitan area, since 1975. A total of 1,094 patients were selected from the database on the basis of having a diagnosis of HF, an ejection fraction of below 40% or unknown, and survived their initial hospitalization for MI. These data were used to model life expectancy as a function of the patient's age, gender and history of diabetes, HF, hypertension, and MI.

This population is not directly comparable to that of EPHEUS because patients' enrollment started in 1993. Consequently, the environment in which life expectancy is estimated is different than what would be expected for patients currently, although not to the same extent as in the Framingham case. Further, patients in this study are comparable to those enrolled in EPHEUS because both groups had HF following MI.

All three sources were used to estimate or model the life expectancy of the EPHEUS patients according to their baseline characteristics because no single source perfectly met these criteria. For the Saskatchewan and Worcester databases, data on 2,543 and 1,094 patients, respectively, with heart failure after an AMI were analyzed with fractional polynomials and piecewise regression to obtain death hazard functions over time [21]. These functions were adjusted according to patient characteristics through the use of separate Cox proportional-hazards models derived from the same data. For patients who died during the trial, life-years lost were obtained by subtracting the in-trial survival times from estimated age- and sex-specific life expectancy estimates [22]. Patients were considered to have 0 life-years lost if they survived during the trial period. Average life-years lost for each treatment group were calculated across all patients who died and survived in each arm of the trial. The difference in average life-years lost because of deaths (placebo minus eplerenone) yields an estimate of the life-years gained with eplerenone.

Based on these estimates, life years lost estimates were calculated as presented in the table below for discount rates varying from 0 to 6%.

Quality adjusted life years (QALYs)

Conceptually, life years gained with low quality of life are less valuable than life years gained with high quality of life. Survival was adjusted for quality of life by multiplying each patient's life years lost by their utility index constructed from the EQ-5D [23] quality of life instrument. The EQ-5D was administered to a subset of patients ($N = 2,280$) in 10 of the 37 countries included in EPHEUS. Of these 2,280 patients, the average response rate across all eight administrations of the EQ-5D (i.e., baseline and months 1, 3, 6, 12, 18, 24, and 30) was 53% for patients in the eplerenone group and 54% for patients in the placebo group. Patients with missing values had their score values imputed using the average score for patients in the same treatment arm with the same follow-up time.

Patients who survived the trial had zero QALYs lost. For patients who died during the trial, QALYs lost were calculated by multiplying that patient's life years lost by the average utility among surviving trial participants in the same treatment arm. For example, if a patient in the eplerenone arm died in month 7, her life years lost would be multiplied by the average utility of all patients in the eplerenone arm measured at month 6. Indirect costs (e.g., costs related to loss of work) and intangible costs (e.g., pain) were not included in this calculation.

Sensitivity analyses

Sensitivity analyses were performed to test the variability of results (i.e., the costs per life-year saved). For simplicity only the medication costs for eplerenone were varied by $\pm 20\%$. We judge these to be the most important, costly parameters. In addition, the discount rate was increased from 3 to 6%.

Results

Table 5 shows the individual costs. These were CHF 16,970 in the group treated with eplerenone and CHF 15,941 in the placebo group. It is evident that there is an additional medication cost of approximately CHF 1,468 per patient over 16 months in the eplerenone group compared to the placebo group in terms of eplerenone costs. In contrast, a savings potential can be seen in the eplerenone group, as the costs of hospitalisations and outpatient procedures were lower. Thus, the total cost difference between the two groups is CHF 1,028.

Table 5 Costs in the eplerenone and placebo groups over 1.3 years (16 months) in Swiss Francs

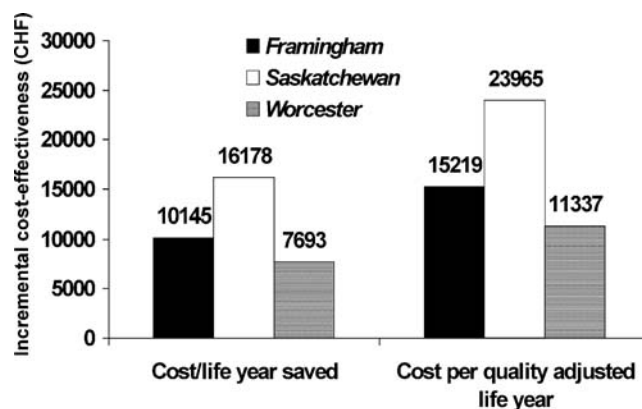
Resource used	Eplerenone	Placebo	Eplerenone– Placebo
Hospitalizations	12,060.17	12,517.25	(457.09)
HF hospitalizations	2,116.53	2,746.99	(630.46)
CV hospitalizations (primary endpoint-based)	3,451.18	4,020.28	(569.10)
All CV hospitalizations	10,920.14	11,380.00	(459.86)
Outpatient procedures	391.87	367.89	23.98
Concomitant medications	3,022.94	3,026.36	(3.43)
Emergency room visits	27.04	29.78	(2.74)
Eplerenone	1,467.76	–	1,467.76
Total	16,969.78	5,941.29	1,028.49

The number of life-years gained with eplerenone treatment was 0.1083 based on Framingham, 0.0661 with Saskatchewan and 0.1518 with Worcester survival estimates. The corresponding incremental gains in QALYs were 0.0722, 0.0446 and 0.1029. (Table 6)

The incremental cost-effectiveness ratio of eplerenone compared with placebo was CHF 10,145 per life-year gained in the analysis using Framingham data. When the Saskatchewan estimates were used, the ICER was CHF 16,178 per life-year gained. Finally the Worcester-based analysis yielded a result of CHF 7,693 per life-year gained. All these estimates are well below the commonly accepted threshold of CHF 50,000 per life-year gained for healthcare interventions in Switzerland, which are covered by third party payers. The corresponding incremental costs per QALY gained were CHF 15,219, CHF 23,965 and CHF 11,337 for the Framingham-, Saskatchewan- and Worcester-based analyses (Fig. 1).

Table 6 Expected additional life expectancy due to eplerenone therapy

	Eplerenone life years lost	Placebo life years lost	Gain in life years with Eplerenone
Life expectancy			
Framingham	−0.57592991	−0.68421821	0.1083
Saskatchewan	−0.32162958	−0.38771208	0.0661
Worcester	−0.69649316	−0.84833168	0.1518
Quality adjusted life expectancy			
Framingham	−0.42124600	−0.49341921	0.0722
Saskatchewan	−0.23362852	−0.27826339	0.0446
Worcester	−0.50919828	−0.61213055	0.1029

**Fig. 1** Overview of cost-effectiveness results.

The results of the sensitivity analysis confirm that the estimated range of incremental cost-effectiveness ratios were between 7,688 and CHF 20,796 per life-year gained and between CHF 8,101 and CHF 30,804 per QALY. Table 7 displays the cost-effectiveness of selected health care interventions.

Discussion

The present economic assessment of eplerenone has proved that the administration of this medication is a highly economically viable option in patients with LVSD after acute myocardial infarctions. The benefits of eplerenone are attributed almost exclusively to the reduction of related hospitalisations. However, the economic performance of a medical intervention can never be judged in isolation, but must always be seen in comparison to other interventions and should be discussed in relation to this background. The positioning of the results in the context of the cost-effectiveness of other interventions is shown in Table 8 and makes it clear that treatment with eplerenone is in a more favourable range, than can be attained by some other broadly accepted interventions.

Our results are similar to those of the cost-effectiveness study, which has been conducted by the original EPHEsus investigators [8]. The number of life-years gained with eplerenone was 0.1014 based on Framingham (95% CI, 0.0306 to 0.1740), 0.0636 with Saskatchewan (95% CI, 0.0229 to 0.1038), and 0.1337 with Worcester (95% CI, 0.0438 to 0.2252) data. Cost was 1,391 dollars higher over the trial period in the eplerenone arm (95% CI, 656 to 2,165) because of drug cost. The incremental cost-effectiveness ratio was 13,718 dollars per life-year gained with Framingham (96.7% under 50,000 dollars per life-year gained), 21,876 dollars with Saskatchewan, and 10,402 dollars with Worcester.

Table 7 Univariate sensitivity analysis: Effect of variation of key input variables on cost-effectiveness ratios (YOLS and QALY)¹

Variable	Base value	Cost-effectiveness	Framingham		Saskatchewan		Worcester	
			Lower estimate ^a	Upper estimate ^a	Lower estimate ^a	Upper estimate ^a	Lower estimate ^a	Upper estimate ^a
Eplerenone costs	1,468	CHF/YOLS	7,250	13,041	11,560	20,796	5,497	9,888
		CHF/QALY	10,875	19,563	17,125	30,804	8,101	14,573
Hospitalization costs	(457)	CHF/YOLS	11,047	9,244	17,616	14,740	8,376	7,009
		CHF/QALY	16,572	13,866	26,095	21,834	12,345	10,330
Outpatient procedure costs	19	CHF/YOLS	10,098	10,193	16,103	16,253	7,657	7,729
		CHF/QALY	15,148	15,290	23,853	24,076	11,284	11,390
Concomitant medications costs	(3.43)	CHF/YOLS	10,152	10,139	16,189	16,167	7,698	7,688
		CHF/QALY	15,299	15,209	23,980	23,949	11,345	11,330
Emergency room visits costs	(2.74)	CHF/YOLS	10,151	10,140	16,187	16,170	7,697	7,689
		CHF/QALY	15,227	14,211	23,977	23,952	11,343	11,331
Discount rate ^b	3%	CHF/YOLS	9,498	10,801	15,564	16,782	6,774	8,639
		CHF/QALY	14,250	16,200	23,042	24,972	9,992	12,729

^a Lower estimate: −20%, upper estimate: +20%^b Lower estimate: 0%, upper estimate: 6%¹ All prices adjusted to 2005

A limitation of the present analysis is certainly that the results of the EPHEsus study, which was conducted in several countries across Europe, Latin America, the United States and Canada, were transferred to the Swiss healthcare setting. Hence, we had to

adjust our calculations, including the estimated life expectancy of patients in Switzerland in order to determine cost-effectiveness. EQ-5D was also only administered to a subgroup of patients in EPHEsus, which gives potential for biases in the QALYs. There

Table 8 Cost-effectiveness of selected cardiovascular interventions in Switzerland

Intervention	Cost per life-year saved in Swiss Francs	Source
Lisinopril in congestive heart failure (ATLAS)	<0*	Ess and Szucs [25]
Captopril after myocardial infarction (SAVE)	1,600	Szucs et al. [26]
Atorvastatin in patients with ACS	3,075	Szucs and Meier [27]
Beta-blockers for post-myocardial infarction patients at high risk	3,600	Goldman et al. [28]
Pravastatin therapy for CHD patients with slightly increased cholesterol values (LIPID)	6,985	Szucs et al. [29]
Eplerenone in patients with leftventricular dysfunction after AMI (EPHEsus)	10,145	Present study
Pravastatin therapy for CHD patients with increased cholesterol values (PLAC I/II)	12,800	Berger K, Klose G, Szucs TD [37]
Low cholesterol diet for men aged ≥60 years with a cholesterol value of 180 mg/dl (4.7 mmol/l)	14,480	Taylor et al. [30]
Amlodipine therapy for CHD patients with normal cholesterol (PREVENT)	14,650	Cathomas et al. [31]
Perindopril in patients with CHD (EUROPA)	17,131	Szucs and Darioli [32]
Pravastatin therapy for CHD patients over 60 years with normal cholesterol values (CARE)	18,400	Berger K, Klose G, Szucs TD [37]
Antihypertensive agents for patients aged ≥40 years with diastolic blood pressure levels ≥105 mm Hg	19,280	Stason and Weinstein [33]
Beta-blockers for post-myocardial patients at low risk	20,400	Goldman et al. [28]
Hypertensive patients with multiple risk factors (ASCOT)	20,003	Szucs et al. [34]
Clopidogrel in coronary secondary prevention (CAPRIE)	24,705	Haldemann et al. [35]
tPA for myocardial infarction (GUSTO IV)	39,440	Mark et al. [36]

* Values < 0 denotes net savings, i.e., a dominant economic strategy

are indications that the influence of other risk factors may possibly vary in the degree of severity to which they affect the Swiss population compared with the original study population. However, the patient population of the EPHESUS study is comparable to a Swiss AMI population with respect to age, co-morbidity and concomitant medication [24]. It should also be pointed out that patients in the EPHESUS study are only partly representative of the total collective of corresponding patients in Switzerland. We also consider life expectancies between Europe and North America to be similar. Unfortunately no life expectancy is provided by Framingham database for individuals with CHF younger than 60. In EPHESUS, if a patient died before 60, the life expectancy for age 60–70 was used. As always, study patients are naturally carefully selected in terms of co-morbidity, compliance and quality of care. In this respect, the results of the EPHESUS study correspond to the best-case scenario.

Another limitation may be the issue of extrapolating costs beyond the scope of the clinical trial. In the EPHESUS US economic analysis, costs were estimated beyond the trial period based on projections of costs within the trial period and life expectancy. This would be technically very difficult in Switzerland. In the US, when costs were extrapolated beyond the trial period, the ICER went up by about 50%. Similar results may be expected in Switzerland, but it is uncertain. Additionally, in EPHESUS, the EQ-5D was only administered to 2,280 patients from 10 of the 35 enrolling countries. We realized that this is a limitation, and used cost per QALYs gained as sensitivity analysis.

Economic evaluations are of practical relevance for the general practitioner to the extent that the conscious use of economical medical therapies reduces their fear and uncertainty about budget adherence and recourse, and justifies his prescribing practice. In particular in the field of cardiovascular interventions there is a need for clinical and economical rationing due to the increased availability of treatment options. The use of cost-effective medical therapies offers the individual doctor some relief for their medication budget, e.g., by reducing the prescriptions of concomitant medications, and a greater individual manoeuvrability within the framework of the fixed prescription budget allocated to them. In addition, economic evaluation can be used as an explicit tool to ensure “value for money” where scarce resources have become a constant threat to the overall health care expenditures.

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Appendix

Table A1 Unit costs outpatient procedures

Description	Local unit cost
Pacemaker, insertion or replacement of pacemaker pulse generator only; single chamber, atrial or ventricular	1,094.23
Insertion or repositioning of electrode lead(s) for single or dual chamber pacing cardioverter-defibrillator and insertion of pulse generator	1,024.72
Myocardial perfusion imaging; (planar) single study, at rest or stress (exercise or pharmacologic), with or without quantification	141.98
Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel	1,526.13
Percutaneous transluminal coronary balloon angioplasty; single vessel	2,289.20
Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; tracing only without interpretation and report	385.29
Electrocardiographic monitoring for 24 h by continuous original ECG waveform recording and storage, and visual superimposition scanning, recording.	172.69
Right heart catheterization	561.25
Left heart catheterization	995.89
Electrophysiologic follow-up study with pacing and recording to test effectiveness of therapy, including induction or attempted induction of arrhythmia	1,067.65
Upper gastrointestinal endoscopy, simple primary examination (e.g., with small diameter flexible endoscope) separate procedure	341.69
Computed tomography, head and brain; without contrast material	108.40
Magnetic resonance (e.g., proton) imaging, orbit, face, and neck; without contrast material(s)	209.33
Magnetic resonance (e.g., proton) imaging, brain (including brain stem); without contrast material(s)	226.27
Radiologic examination, chest; single view, frontal	39.21
Computed tomography, thorax; without contrast material	136.31
Magnetic resonance (e.g., proton) imaging, any joint of lower extremity; without contrast material	245.44

Table A1 (continued)

Description	Local unit cost
Computed tomography, abdomen; without contrast material	136.31
Magnetic resonance (e.g., proton) imaging, abdomen; without contrast material	204.83
Cardiac magnetic resonance imaging for morphology; without contrast material	263.93
Ultrasound, abdominal, B-Scan and/or real time with image documentation; complete	112.52
Electrocardiogram, routine ECG with at least 12 leads; tracing only without interpretation or report	32.32
Transthoracic echocardiography for congenital cardiac anomalies; complete	131.28
Echocardiography, transthoracic, real time with image documentation (2D), with or without M-mode recording during rest and cardiovascular stress test	368.24

Table A2 Unit cost: hospitalisation

Description	Local unit cost
Specific cerebrovascular disorders except TIA	14,705.48
Coronary bypass with PTCA	50,000.00
Coronary bypass W cardiac CATH	44,476.76
Percutaneous cardiovascular procedures	10,000.00
Other PERM cardiac pacemaker implant or PTCA W coronary ART stent	12,231.73
Circulatory disorders W AMI W/O major COMP DISCH alive	12,760.27
Heart failure & shock	14,810.10
Cardiac arrhythmias & conduction disorders W/O CC	3,084.27
Angina pectoris	5,731.73
Other infectious & parasitic diseases diagnoses	8,499.66
Other disorders of nervous system w/o cc	3,356.40
Chronic obstructive pulmonary disease	14,935.20
Simple pneumonia & pleurisy age >17 w/o cc	9,047.86
Other respiratory system diagnoses w/o cc	3,269.42
Heart transplant	80,000.00
Cardiac valve & oth major cardiothoracic proc w/o card cath	56,499.86
Prm card pacem impl w ami/hr/shock or aicd lead or gntrr	56,499.86
Other circulatory system o.r. procedures	27,473.15
Cardiac arrest, unexplained	5,302.68
Peripheral vascular disorders w/o cc	8,466.42

Table A2 (continued)

Hypertension	6,487.61
Syncope & collapse w/o cc	3,000.86
Chest pain	2,277.39
Other circulatory system diagnoses w/o cc	4,156.36
Esophagitis, gastroent & misc digest disorders age >17 w/o cc	3,050.19
Other musculoskelet sys & conn tiss o.r. proc w/o cc	8,029.15
Diabetes age >35	13,378.89
Renal failure	14,225.32
Other kidney & urinary tract diagnoses age >17 w/o cc	1,951.41
Red blood cell disorders age >17	8,340.36
Reticuloendothelial & immunity disorders w/o cc	4,374.16
Traumatic injury age >17 w/o cc	6,079.53
Allergic reactions age >17	2,259.40
Complications of treatment w/o cc	3,091.89

cc: complications

Table A3 Unit cost: medication

Drug name	Local cost per day (CHF)
Abciximab in male	1,686.71
Abciximab in female	1,472.04
Acetaminophen	0.72
Allopurinol	4.15
Amiodarone	0.76
Amlodipine	1.47
Aspirin	0.19
Atenolol	4.23
Atorvastatin	2.24
Bisoprolol	4.56
Captopril	4.61
Carvedilol	0.80
Clonidine	2.00
Clopidogrel	3.26
Digoxin	0.10
Enalapril	0.94
Fenofibrate	0.95
Fosinopril	1.44
Furosemide	0.33
Glyburide	
Hydrochlorothiazide	0.35
Ibuprofen	0.57
Insulin	4.86
Isosorbide Dinitrate	0.51
Isosorbide Mononitrate	0.84
Levothyroxine	0.16
Lisinopril	0.56
Losartan	1.58
Magnesium	0.40
Metformin	0.29
Metoprolol	0.65
Molsidomine	0.57
Nitroglycerin	1.78

Table A3 (continued)

Drug name	Local cost per day (CHF)
Omeprazole	1.59
Perindopril	1.27
Potassium Chloride	0.93
Pravastatin	2.03
Ramipril	1.23
Ranitidine	1.70
Rofecoxib	
Simvastatin	1.51
Trandolapril	0.98
Warfarin	0.77

References

- Dargie HJ, McMurray JJ, McDonagh TA. Heart failure—implications of the true size of the problem. *J Intern Med* 1996;239(4):309–15.
- Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J* 1999;20(6):447–55.
- Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;24(5):442–63.
- Cleland JG, Gemmell I, Khand A, Boddy A. Is the prognosis of heart failure improving? *Eur J Heart Fail* 1999;1(3):229–41.
- Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208–25.
- Szucs T. [Health economic aspects of chronic heart failure. Part 1: Burden of disease and economic appraisal.] *Gesundheitsökonomische Aspekte der chronischen Herzinsuffizienz. Teil 1: Krankheitslast und ökonomische Bewertung. Schweizerische Ärztezeitung* 2003;84(46):2431–5 (www.saez.ch; last accessed July 5, 2005)
- Szucs TD. The growing healthcare burden of CHF. *J Renin Angiotensin Aldosterone Syst* 2000 Sep;1(Suppl 1):2–6
- Weintraub WS, Zhang Z, Mahoney EM, Kolm P, Spertus JA, Caro J, Ishak J, Goldberg R, Tooley J, Willke R, Pitt B. Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. *Circulation* 2005;111(9):1106–13.
- Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348(14):1309–21.
- Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, Neaton J, Roniker B, Hurley S, Burns D, Bittman R, Kleiman J. The EPHEsus trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone post-AMI heart failure efficacy and survival study. *Cardiovasc Drugs Ther* 2001;15(1):79–87.
- Schulman K, Burke J, Drummond M, Davies L, Carlsson P, Gruger J, Harris A, Lucioni C, Gisbert R, Llana T, Tom E, Bloom B, Willke R, Glick H. Resource costing for multinational neurologic clinical trials: methods and results. *Health Econ* 1998;7(7):629–38.
- Casemix E. Main results of the Swiss study on DRGs (Casemix Study). *Soz Praventivmed* 1989;34(4):156–66.
- www.tarmed.ch (last accessed April 2005)
- Arzneimittelkompendium der Schweiz (Swiss Formulary), Documed, Basel, 2005.
- Mahoney EM, Jurkovic CT, Chu H, Becker ER, Culler S, Kosinski AS, Robertson DH, Alexander C, Nag S, Cook JR, Demopoulos LA, DiBattiste PM, Cannon CP, Weintraub WS; TACTICS-TIMI 18 Investigators. Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *JAMA* 2002;288:1851–8.
- Peeters A, Mamun AA, Willekens F, Bonneux L. A cardiovascular life history. A life course analysis of the original Framingham Heart Study cohort. *Eur Heart J* 2002;23:458–66.
- Franco OH, Peeters A, Bonneux L, de Laet C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: Life course analysis. *Hypertension* 2005;46:280–286.
- Downey W, Beck P, McNutt M, Stang MR, Osei W, Nichol J. Health databases in Saskatchewan. In: Strom BL, editor. *Pharmacoepidemiology*, 3rd ed. Chichester: Wiley; 2000. p. 325–45.
- Goldberg RJ, Yarzebski J, Lessard D, Gore JM. A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective. *J Am Coll Cardiol* 1999;33:1533–39.
- Spencer FA, Meyer TE, Goldberg RJ, Yarzebski J, Hatton M, Lessard D, Gore JM. Twenty year trends (1975–1995) in the incidence, in-hospital and long-term death rates associated with heart failure complicating acute myocardial infarction: a community-wide perspective. *J Am Coll Cardiol* 1999;34:1378–87.
- Blackstone EH, Naftel DC, Turner MEJ. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc* 1986;81:615–24.
- Mahoney EM, Jurkovic CT, Chu H, Becker ER, Culler S, Kosinski AS, Robertson DH, Alexander C, Nag S, Cook JR, Demopoulos LA, DiBattiste PM, Cannon CP, Weintraub WS, for the TACTICS-TIMI 18 Investigators. Treat Angina with Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction: cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *JAMA* 2002;288:1851–58.
- Rabin R, De Charro F. EQ-5D: a measure of health status from the EuroQoL group. *Ann Med* 2001;33:337–43.
- Erne P, Radovanovic D, Urban P, Stauffer J-C, Bertel O, Gutzwiller F. Early drug therapy and in-hospital mortality

- following acute myocardial infarction. *Heart Drug* 2003; 3:134–40.
25. Ess SM, Szucs TD. High dose lisinopril in heart failure: economic considerations. *Cardiovasc Drugs Ther* 2002;16:365–71.
 26. Szucs T, Berger K, Schulte-Hillen J, Kleber FX. Die Wirtschaftlichkeit von Captopril nach Myokardinfarkt. *Med Klinik* 1996;91:112–18.
 27. Szucs TD, Meier B. Kosten-Effektivität von Atorvastatin bei Patienten mit akutem Koronarsyndrom. Eine Analyse der der PROVE-IT Studie. *Kardiovaskuläre Medizin* 2004;7: 412–20.
 28. Goldmann L, Sia STB, Cook EF, Rutherford JD, Weinstein MC. Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. *N Engl J Med* 1988;319:152–57.
 29. Szucs TD, Bertel O, Darioli R, Gutzwiller F, Mordasini R. Ökonomische Evaluation von Pravastatin in der Behandlung der koronaren Sekundärprävention. Eine Analyse auf der Basis der LIPID Studie (Economical and pharmacological valuation of pravastatin in secondary coronary prevention) *Schw Rundschau Med Praxis* 2000;57:1667–73.
 30. Taylor WC, Pass TM, Shephard DS, Komaroff AL. Cost-effectiveness of cholesterol reduction for the primary prevention of coronary heart disease in men. *Preventing disease: Beyond the rhetoric*. New York: Springer; 1990.
 31. Cathomas G, Erne P, Schwenkglenks M, Szucs T. The economic efficiency of Amlodipine on the treatment of coronary Atherosclerosis—an analysis based on the PREVENT study. *Cardiovasc Drugs Ther* 2002;16:61–6.
 32. Szucs TD, Darioli R. Kosten-Effektivität von Perindopril bei Patienten mit koronarer Herzkrankheit in der Schweiz—Eine Analyse der Europa Studie. *Kardiovaskuläre Medizin* 2004;7:443–52.
 33. Stason WB, Weinstein MC. Allocation of resources to manage hypertension. *N Engl J Med* 1977;296:732–9.
 34. Szucs TD, Müller D, Darioli R. Schweizer Analyse der ASCOT-Studie: Wie kosten-effektiv sind Statine in der koronaren Prävention? *Cardiovasc* 2003;5:29–32.
 35. Haldemann R, Lüscher TF, Szucs TD. Die Wirtschaftlichkeit von Clopidogrel in der kardiovaskulären Sekundärprävention: eine Kosten-Effektivitäts-Analyse auf der Grundlage der CAPRIE-Studie. [Cost Effectiveness of Clopidogrel in the Secondary Prevention of Major Cardiovascular Events]. *Praxis* 2001;90:539–45.
 36. Mark DB, Hlatky MA, Califf RM, Naylor CD, Lee KL, Armstrong PW, Barbash GB, White H, Simoons ML, Nelson CL, Clapp-Channing N, Knight JD, Harrell FE, Simes J, Topol EJ. Cost-effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med* 1995;332:1418–31.
 37. Berger K, Klose G, Szucs TD. Economic aspects of drug therapy exemplified by pravastatin. A socioeconomic analysis of cholesterol synthase enzyme inhibition in coronary heart disease patients. *Med Klin* 1997;92:363–9.